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Nicotine's Effect on Attention Deficits in the Schizophrenic Population

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Recommended Citation

Radovich, Nicole and Solai, Radha, "Nicotine's Effect on Attention Deficits in the Schizophrenic Population" (2017). *School of Physician Assistant Studies*. 614.
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Nicotine's Effect on Attention Deficits in the Schizophrenic Population

Abstract

Background: Schizophrenia is a debilitating psychiatric disease that can cause many symptoms including attention deficits and cognitive impairments. Currently there are no effective treatments for the cognitive symptoms in schizophrenia. There is a large population of smoking schizophrenics, which has pushed research to examine a possible correlation between nicotine and schizophrenia. Research has found that a possible cause for this correlation is self-medication: given that nicotine may enhance cognition. Research has now taken it one step further and examined the effect of nicotine administration on attention performance.

Method: An exhaustive search using MEDLINE-PubMed, MEDLINE-Ovid, CINAHL, Google Scholar, and Web of Science was performed using the keywords: schizophrenia, nicotine, patch, and cognition. Eligibility criteria were applied to refine the search further. Articles were assessed for quality using GRADE criteria.

Results: After completing the search, three articles were selected according to the inclusion and exclusion criteria. All studies were RCTs and compared the effects of the transdermal nicotine patch with schizophrenic participants versus controls. One study compared smoking participants, another compared non-smoking participants, and the last one compared both groups. All three studies support the hypothesis that nicotine improves the attention deficits in schizophrenia. The discussed studies focus on short-term effects of nicotine on attention performance, so future research should examine the long-term effects for safety and efficacy.

Conclusion: Administration of a transdermal nicotine patch has been shown to improve attention performance in schizophrenics. If further research validates these findings, usage of transdermal nicotine patches can be considered as an alternative therapy given the ease of use and availability.

Keywords: Schizophrenia, nicotine patch, attention, and cognition

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Keywords

Schizophrenia, nicotine patch, attention, cognition

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Nicotine's Effect on Attention Deficits in the Schizophrenic Population

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A Clinical Graduate Project Submitted to the Faculty of
the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 12, 2017

Faculty Advisor: Craig Turner

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Nicole Radovich is from Northern California and received her Bachelor of Science degree from San Diego State University in 2012 with a major in Public Health. Her background is in physical therapy. She worked as the supervising physical therapy aide at a clinic in Portola Valley, California. She is interested in cardiothoracic surgery and orthopedics.

Radha Solai is from Southern California and received her Bachelor of Arts degree from University of California, Riverside in 2013 with a major in Psychology. Her background is in family medicine. She worked as a medical scribe and medical assistant in a clinic in Imperial Beach, California. She is interested in staying in family medicine with an emphasis in cardiology or psychology.

Abstract

Background: Schizophrenia is a debilitating psychiatric disease that can cause many symptoms including attention deficits and cognitive impairments. Currently there are no effective treatments for the cognitive symptoms in schizophrenia. There is a large population of smoking schizophrenics, which has pushed research to examine a possible correlation between nicotine and schizophrenia. Research has found that a possible cause for this correlation is self-medication: given that nicotine may enhance cognition. Research has now taken it one step further and examined the effect of nicotine administration on attention performance.

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Acknowledgements

To our family: We could not have done this without you. Thank you for supporting us through our journey.

Table of Contents

Biography.....	2
Abstract.....	3
Acknowledgements.....	4
Table of Contents.....	5
List of Tables.....	6
List of Abbreviations.....	6
Background.....	7
Methods.....	8
Results.....	8
Discussion.....	14
Conclusion.....	17
References.....	18
Tables.....	19

List of Tables

Table I. GRADE Quality of Assessment: Characteristic of Reviewed Studies

List of Abbreviations

GRADE	grading of recommendations, assessment, development, and evaluations
RCT	randomized controlled trial
nACHRs	nicotinic acetylcholine receptors
mg	milligram
CPT-IP	continuous performance test identical pairs
LOC	loss of consciousness
D2 blocking	dopamine 2 receptor blocking
CNS	central nervous system
DSM	diagnostic and statistical manual

Nicotine's Effect on Attention Deficits in the Schizophrenic Population

BACKGROUND

Schizophrenia is a psychological disorder that can cause hallucinations, delusions, disordered speech, attention deficits, and other cognitive impairments. Antipsychotics are the mainstay of treatment for schizophrenia; however, there are no effective medications for the attention deficits present in schizophrenia. Medications used in the general population for attention deficits have a possible interaction with the necessary antipsychotics prescribed for schizophrenia. Having attention deficits can cause barriers to educational performance and efficiency in the workplace. This is an issue as almost one-half of homeless adults in America are schizophrenic.¹ By treating attention deficits in schizophrenia clinicians can improve functionality and help patients to better cope with the disease.

A common trend seen amongst the schizophrenic population is high rates of cigarette smoking. As demonstrated by the fact that 58-88% of schizophrenics smoke cigarettes compared to the 23% of the general population.² Previous research has focused on determining the correlation of smoking in schizophrenia sufferers. Studies have found that the cause could be due to possible self-medication as nicotine seems to help improve cognitive symptoms in schizophrenia.² Nicotine mimics acetylcholine, which binds to nicotinic receptors in the brain. These receptors are involved in cognition including attention. Preclinical trials have shown that repeated administration of nicotine causes an up-regulation of nAChRs,³ which improves the attention deficits.

Many trials have examined the effect of medications such as acetylcholinesterase

inhibitors, nAChR agonists, and nicotine administration that effect nAChRs. There is limited support regarding the efficacy of acetylcholinesterase inhibitors and nAChR agonists.⁴ There is more support behind use of nicotine administration including transdermal patch, gum, and nasal sprays. Nicotine administration is also safe, cheap, and easy to administer. Use of nicotine administration through gum or nasal spray could possibly cause differing levels of nicotine extraction.⁴ Because of this, the effects of a transdermal nicotine patch in correlation to schizophrenic attention performance are examined. The goal of this review is to assess the use of transdermal nicotine patch to improve attention in the schizophrenic population.

METHODS

An exhaustive literature review was performed by searching MEDLINE-PubMed, MEDLINE-Ovid, CINAHL, Google Scholar, and Web of Science databases. The following keywords were used to help narrow down the results: schizophrenia, nicotine, patch, attention, and cognition. Reviewed articles were also used as a source for allocation of other relevant articles. Inclusion criteria consisted of randomized controlled trials studying a population of patients with clinically diagnosed schizophrenia as defined by the DSM IV or V, comparing transdermal nicotine patches to a placebo or absence of nicotine patch, and measuring attention deficits. Exclusion criteria consisted of articles not written in the English-language, that enrolled participants who were younger than 15 years, and that had a sample of less than 25 participants. All relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation.⁵

RESULTS

A total of 93 articles were found initially from database search. From the 93 articles 10

fit the eligibility criteria. Three articles out of the 10 were selected for review. All three articles are randomized controlled studies and each examined a different population. One article focused on smoking schizophrenics,⁴ another focused on non-smoking schizophrenics,⁶ and the last article compared both populations.⁷

Jacobsen et al

In 2004, Jacobsen et al⁴ conducted a randomized double blind trial examining the effects of nicotine on brain function in smoking schizophrenics compared to smoking controls. The primary outcome of this trial was attention and memory. Participants were assessed by completing tasks while receiving an fMRI scan.⁴

There were 26 total participants in this study and all were smokers. There were 13 participants who were schizophrenic and 13 who were controls. Recruitment of participants was not discussed throughout the study. Inclusion criteria were not stated as well. Exclusion criteria included history of head trauma, medical illnesses compromising the CNS, substance or alcohol abuse within 12 months, and diabetes.⁴

There were 2 trials performed in this study. All participants received both a transdermal nicotine patch and a placebo patch. Order of administration was randomized and double blind. Dosing of transdermal nicotine patch depended upon BMI. Participants with a BMI less than 26 kg/m² received a 28 mg nicotine patch and those with a BMI more than 26 kg/m² received a 35 mg nicotine patch. Scanning was done 6 hours after application of patch. During scanning participants performed an auditory n-back test with 2 levels of working memory load and 2 levels of selective attention load. Participants either heard a phrase in both ears or different phrase in each ear (dichotic). They were then told to identify if the phrase was 1-back which is a

back-to-back repeat of a word or a 2-back which is a repeat that is separated by a different word. A total of 120 echoplanar functional images were taken per slice during the tasks.⁴

Results showed that nicotine improved performance in schizophrenic participants. Specifically, there was more activation in different parts of the brain during the dichotic 2-back tasks while using nicotine in schizophrenic participants versus controls ($p=0.03$). Dichotic 2-back tasks were the most difficult to perform which shows the extent of the effect of nicotine. Also, regions of the brain showed more of an increase in activity in the nicotine patch trials during the high selective attention load with schizophrenic participants ($p<0.01$).⁴

Limitations of this study include that all non-smokers were excluded. There is a possible confounder called the relief-from withdrawal phenomenon, which states that the cognitive enhancement seen in smokers using nicotine replacement could be due to relieving withdrawal symptoms instead of increasing cognitive function.⁸ The sample size was quite small, so there is a threat to precision of the outcome. Also, the chemical breakdown of nicotine (plasma cotinine) and serum nicotine was higher in schizophrenic participants versus controls before administration of patches. This could pose a possible confound as to why they performed superior to controls.⁴

Barr et al

Barr et al⁶ conducted a randomized, double-blinded, placebo-controlled, crossover trial in 2008 examining the effects of transdermal nicotine patch on cognition in nonsmokers with schizophrenia versus nonsmoker controls. The primary outcome focused on in this trial was attention performance, which was assessed by using CPT-IP testing.⁶

Schizophrenic participants in the study were recruited from an urban community mental

health clinic. Control participants were enlisted from advertising in both local press and on the internet. Inclusion criteria included participants aged 18-65 years, non-smokers for over 3 months prior to enrollment, and patients with diagnosis of schizophrenia or schizoaffective disorder by DSM IV. Exclusion criteria included substance abuse or dependence, any lifetime diagnosis of cognitive impairment secondary to head injury, dementia, use of investigational medication in the past month, current diagnosis of major depressive disorder, current unstable medical illnesses, and any recent schizophrenia medication changes or changes in disease. There were 60 total participants who met criteria, 28 were schizophrenic and 32 were controls.⁶

Three visits were conducted in this study. The first visit was intended to set a baseline for participants and training. Participants were then randomized blindly using a computer generated random number sequence. This was done to determine which patch they received first, active patch or placebo patch. The next 2 visits were separated by 1-2 weeks. Participants received either 2 patches of the 7 mg transdermal nicotine or placebo and then completed CPT-IP testing 3 hours later. During testing, participants were asked to identify 2 identical pairs in sequence by clicking the computer mouse with their dominant hand. The following outcomes were measured: signal to noise, correct hits, hit time reaction, standard deviation of hit time reaction, and errors such as false alarms.⁶

Results of the repeated measures ANOVA showed improved performance for both groups using a nicotine patch. There was a reduced hit reaction time ($p < 0.0001$) and reduced random errors ($p < 0.001$). In addition, there were greater reductions with schizophrenic participants taking nicotine patch. The calculated 95% confidence interval was 342-742 with a

mean of 542 for schizophrenic participants after placement of nicotine patch. Findings were statistically significant.⁶

Limitations of this study are that only non-smokers were included in order to prevent confounders. Previous research focused on studying smokers exclusively and found that the nicotine patch could be treating withdrawal symptoms instead of improving cognition. Because of this, the focus of this study is on non-smokers. However this can be a limitation, as both groups were not compared in this study. Also the control group had participants that were significantly younger, had a higher IQ, and a lower rate of previous smoking. In addition, medications taken by schizophrenics were not controlled. Nicotine could be improving impairments caused by anti-psychotic medications rather than improving schizophrenic attention deficits.⁶

Petrovsky et al

Petrovsky et al⁷ conducted a randomized, double-blinded, placebo-controlled, crossover study in 2013 examining the effects of nicotine on oculomotor performance. This study compared 4 groups including smoking schizophrenics, non-smoking schizophrenics, smoking controls, and non-smoking controls. They used oculomotor testing as a surrogate outcome for attention performance.⁷

Schizophrenic participants were recruited from the outpatient clinic of the University Hospital, Bonn. Controls were recruited from local advertisements and city registry. Inclusion criteria were: smokers and non-smokers, both male and female participants, ages 15-55 years old, and participants diagnosed with schizophrenia or schizoaffective disorder according to DMS IV. Exclusion criteria included: head injury with LOC > 5 min, life-time history of alcohol or

substance abuse dependence, history of neurologic illness or other severe medical condition, clinical instability, recent change in medication <6 weeks, anticholinergic medication, severe obesity of a BMI >30 kg/m², and uncorrected visual impairments. There were 48 total participants after applying the criteria. There were 22 schizophrenic participants, consisting of 12 smokers and 10 non-smokers. There were 26 controls, consisting of 14 smokers and 12 non-smokers.⁷

This study included a total of 2 testing days. Each participant had 1 trial with placebo patch and 1 trial with nicotine patch. The order of which patch came first was randomized. The patches were dosed dependent upon whether the participant smoked or did not smoke. Participants who smoke received a 14 mg transdermal nicotine patch and non-smoking participants received a 7 mg transdermal nicotine patch. Oculomotor testing was completed 3 hours after application of patch. Oculomotor, or saccadic eye movement, is under control of the executive functioning of the brain and it is used to estimate attention performance. Tasks completed during oculomotor testing consisted of performing 1 block of both standard and delayed antisaccade and prosaccade trials. During standard trials, participants were told to fixate on a center cross and subsequently a target dot and wave tone would appear in the periphery. Participants were told to then move their eyes either towards the target in the prosaccade trials or away from the target in the antisaccade trials. In delayed trials the peripheral target would appear in the periphery but participants were told not to move their eyes until the delayed wave tone appears.⁷

Nicotine reduced errors during standard antisaccade trials in both controls and schizophrenic participants equally ($p=0.02$). Because of this, antisaccade performance was

found to be improved. There was no correlation between prior smoking status and antisaccade performance ($p=0.10$). This implies that nicotine has an equal effect on cognitive performance in both smoking and non-smoking participants. Antisaccade latencies were decreased in the nicotine trials ($p = 0.0003$), which suggests improved attention performance. Antisaccade error rate was positively correlated with plasma cotinine levels in standard trials ($p = 0.02$). This data implies there is a dose dependent response with nicotine and antisaccade performance.⁷

Limitations of this study include using surrogate outcomes. Oculomotor testing has been shown to be an effective testing measure for cognitive function but is not specific to attention. Because this is not a direct measure there is some indirectness of the results. In addition, the range of saccade eye movement was so narrow that a small change could be considered statistically significant. This can make the outcomes seem larger than they really are. Lastly, smoking participants were deprived of smoking overnight so there is a possibility for relief of withdrawal symptoms versus true cognitive enhancement. Petrovsky et al suggests future research to have smoking participants deprived for only 2 hours compared to overnight.⁷

DISCUSSION

All studies^{4,6,7} reviewed suggest an increase in attention performance with nicotine patch in schizophrenic populations. This provides the starting point to establishing a simple form of treatment for attention deficits in schizophrenics. Jacobsen et al⁴ found that non-smoking schizophrenics and controls had increased brain activity and attention performance with 14-gram nicotine patch administration. Barr et al⁶ found that smoking schizophrenics and controls had improved attention performance with nicotine patches dosed based upon BMI. Petrovsky et al⁷ compared both nonsmoking and smoking schizophrenics and controls. This

study found that schizophrenics had an increased performance with nicotine patch dosed dependent upon smoking status. These three studies show there is a possible correlation between the usage of a nicotine patch and improving attention deficits in both non-smoking and smoking schizophrenics. Because of these results, administration of transdermal nicotine patch could be considered for off-label treatment of cognitive symptoms in schizophrenia after additional research is conducted.

There was some variability across studies including the amount of nicotine given in each patch and type of testing administered. Jacobsen et al⁴ used a patch based on BMI and the results of this study only showed improvement in schizophrenic participants rather than all groups as found in Petrovsky et al⁷ and Barr et al.⁶ Petrovsky et al⁷ dosed based upon smoking status and Barr et al⁶ used a standard 14 mg transdermal patch for all groups. Given there was variability on dosing of transdermal nicotine patch in all three studies, future research should focus on determining adequate dosing of therapeutic nicotine patch. In addition, all three studies included different types of cognitive testing administered and could provide some variation in the results. It is hard to compare such differing cognitive testing especially with surrogate testing in Petrovsky et al⁷ in comparison to the direct testing measures used in Barr et al⁶ and Jacobsen et al.⁴ There is some benefit in using different measures to assess the cognitive function in that attention is a broad skill; however, it is difficult to assess whether all testing is measuring the same cognitive components.

There is also a risk of bias considering the small sample size of all studies reviewed. Using a small sample size poses the risk of not representing the schizophrenic population accurately. With a small sample size study results can be found to not be statistically significant

because small changes cause larger deviations. Petrovsky et al⁷ possibly has a risk of selection bias given schizophrenic participants were only recruited from the out-patient clinic of the University Hospital, Bonn. Barr et al⁶ has a risk of selection bias as schizophrenic participants were only recruited from the out-patient population of an urban community mental health clinic. Jacobsen et al⁴ did not specify where participants were recruited from so bias cannot be ruled out. Future research should focus on studying a more diverse and larger sample size.

There are also some major confounders in the discussed studies. Firstly schizophrenic participants were taking different types and doses of D2 blocking anti-psychotics in each study. Different doses of dopamine antagonists can cause different levels of cognitive enhancement from nicotine. Also, nicotine could be treating the dopamine antagonist related to cognitive deficits rather than schizophrenic specific cognitive deficits.⁶ Future research should control for this or study the interaction between dopamine antagonists and nicotine. Another confounder is the relief-from withdrawal phenomenon. As previously stated, this implies that using nicotine replacement in smokers may be helping withdrawal symptoms rather than being true cognitive enhancers.⁶ Future research should take this into account when studying the smoking populations and provide less time deprived of smoking before testing.

In addition, all studies discussed only examine the short-term effects of nicotine on cognition and attention.³ Smokers develop tolerance to nicotine overtime so the attention effects seen in these studies may not last. If tolerance does occur with therapeutic nicotine patch administration, providers would have to continue to increase dosage and there could be risks with this. Nicotine patches are currently used for smoking cessation as short-term therapy so the long-term effects have not been established. Future research should emphasize long-

term efficacy and safety of nicotine.

Clinicians could consider the possibility of nicotine patches as therapeutic treatment for attentional symptoms of schizophrenia once future research has defined dosing and long-term effects. Usage of the transdermal nicotine patch could provide an easy and inexpensive way to support schizophrenic attention deficits in order to improve their functionality in society. Usage of transdermal nicotine patch can also help with smoking cessation in the schizophrenic population. By addressing attention symptoms providers can prevent the self-medication through cigarette smoking and decrease the many complications that come along with smoking. Overall transdermal nicotine patches could be considered as a reasonable treatment option after research studies the relationship between schizophrenia and nicotine in depth.

CONCLUSION

According to the articles reviewed, nicotine patch administration has a positive correlation with attention performance in the schizophrenic population. The long-term effects are not clearly established but research suggests short-term improvement of schizophrenic attention deficits. This correlation has been shown to occur in both smoking and non-smoking schizophrenics, which indicates nicotine as a true attention enhancer. Results did not indicate a profound change in performance; however, all three studies resulted in some improvement in attention, which suggests reliable outcomes. Future research is warranted to validate this correlation, identify proper dosing, and examine long-term effects of nicotine administration. By continuing to research on this possible method of treatment we can improve functionality in society and in turn decrease the high incidence of homelessness and cigarette smoking in the schizophrenic population.

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TABLES

Table 1: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Jacobsen et al ³	RCT	Serious ^a	Not Serious	Not Serious	Serious ^b	Unlikely	N/A	Low
Barr et al ⁶	RCT	Not Serious	Not Serious	Not Serious	Not Serious	Unlikely	N/A	High
Petrovsky et al ⁷	RCT	Not Serious	Serious ^c	Not Serious	Serious ^b	Unlikely	Dose response gradient	Moderate
^a Didn't address confounders related to withdrawal symptoms ^b Small sample size was used ^c Surrogate outcomes were used								